Declaration

I, Mark Cregan, hereby declare and state:

THAT I am one of the inventors of the invention disclosed and claimed in the present application, and that I previously submitted a Declaration dated August 20, 2008 in the present application, the entire content of which is incorporated herein by reference;

THAT I have reviewed the outstanding Office Action from the US-Examiner dated February 26, 2009 in the above referenced application, especially the Examiner's comments with regard to the prior art, especially Young et al. (Aus. J. Zool. 45:423-433; 1997) and Stingl et al. (Breast Cancer Res. Treat. 67:93-109; 2001).

THAT I continue to conclude that none of the prior art references, alone or in combination, teach or suggest my invention as set forth in the currently pending claims;

THAT, I continue to conclude that the prior art references are incompatible with each other and are not combinable in a manner that would lead to my invention, as detailed subsequently;

THAT, at least because the prior art does not have a teaching of the isolation of pluripotent progenitor cells from human mammary secretion by the Examiner's own admission, the claims should be found allowable.

Amended claims 1 and 18, among other features, specify that the progenitor cells are isolated from human mammary secretion, and that they are pluripotent cells.

1. Arguments for novelty and non-obviousness of claim 18:

The examiner states in page 6 of the above mentioned office action that, even though the product was made by a different process, the claim is unpatentable if the product is the same as or obvious from a product of the prior art. I am of the opinion that the claimed product, i.e. pluripotent progenitor cells isolated from human mammary secretion, is new over the cited document, Stingl et al., for the following reasons:

Stingl et al.:

Stingl describes the isolation of primitive epithelial precursor cells from mammary tissue.

The three cell types isolated in Stingl et al. are cells capable of developing into a) luminal epithelial cells, b) myoepithelial cells, or c) bipotent cells still capable of developing into either luminal epithelial cells or myoepithelial cells (in other words, precursors of a) and b)). The three types of cells thereby identified are all of *epithelial* character (committed/specialized to differentiate into cells of an epithelial cell line).

Present invention:

The present invention according to claim 18 is directed to pluripotent progenitor cells isolated from human mammary secretion, in other words, cells which are not yet committed to a specific lineage, organ, or tissue.

Some definitions of "pluripotency":

According to the National Institute of Health, there are three classes of stem cells: totipotent, pluripotent and multipotent. A fertilized egg is considered totipotent, meaning that its potential is total; it gives rise to all the different types of cells in the body. Pluripotent stem cells can give rise to any type of cell in the body except those needed to develop a fetus. Stem cells that can give rise to a small number of different cell types are generally called multipotent.
(http://stemcells.nih.gov/StemCells/Templates/StemCellContentPage.aspx?NRMODE=Published&NRNODEGUID={A604DCCE-2E5F-4395-8954-FCE1C05BECED}&NRORIGINALURL=%2finfo%2ffaqs.asp&NRCACHEHINT=NoModifyGuest#classes).

According to another source, pluripotent cells are generally defined as stem cells, which are derived from totipotent stem cells and have the ability to differentiate into any cell type of an organism, and can develop into various cells, tissues, or organs (except the cells of the placenta or other supporting tissues of the uterus). They cannot, however, develop into an intact individual organism (as compared to totipotent stem cells). Multipotent cells are defined as stem cells (only) having the ability to differentiate into various cells of a particular cell lineage (as compared to pluripotent stem cells).

(http://www.lifecellinternational.com/power-of-stem-cells-and-cord-blood/what-are-stem-cells/types-of-stem-cells).

In the context of the application itself (see page 1, lines 16-23 of the specification), pluripotent cells are defined as embryonic stem cells which are capable of generating into all differentiated cells types within the body. Pluripotent cells, also called embryonic stem cells,

differ from multipotent cells, also called adult stem cells, in that multipotent cells are derived from pluripotent cells and are organ- or tissue specific.

Differences of claim 18 to Stingl et al.:

In my opinion, the cells disclosed in Stingl et al. can not be categorized as "pluripotent" cells any longer, as they are already differentiated far enough to be specialized. The cells of the type c) noted above are said to be bipotent (able to differentiate into two different cell types a) and b), thus having two possible fates), which implies that types a) and b) are monopotent (one possible fate). While Stingl talks about monopotent and bipotent tissue-specific progenitor cells (committed to epithelial tissue), he focuses his disclosure not only on tissue-specific progenitor cells, but within this narrow selection also on mono- and bipotent types thereof (as tissue-specific progenitor cells as such could also have more than two different fates within the same tissue, i.e. be tripotent). In contrast, my invention does not concern mono- or bipotent tissue-specific progenitor cells which are committed to a mammary gland-specific pathway, and not even the group of just tissue-specific progenitor cells in general, but it concerns progenitor cells which are not yet committed to a specific lineage, organ or tissue.

The cells isolated in Stingl et al. were "postulated" to represent a mammary epithelial stem cell compartment. However, this, in my view, is a false postulation, as cells already committed to a specific cell lineage, such as the epithelial cell lineage, can no longer be defined as "stem cells", but at the most as precursor- or progenitor cells, if at all. In page 94 (left column, 3rd paragraph) of Stingl, it is said that the results obtained in the study demonstrate the existence in adult human mammary tissue of phenotypically distinct subpopulations of progenitor cells. This is another indication that these progenitor cells cannot be pluripotent stem cells, as "phenotypically distinct subpopulations" do not encompass pluripotent stem cells. As already mentioned above, Stingl merely describes the discovery of mono- and bipotent epithelial-specific progenitor cells. In my view, Stingl uses stem cell terminology in a rather loose and unprofessional way, which can easily confuse a reader not familiar with stem cell biology, and lead him away from the actual very narrow scope of disclosure of the paper.

Furthermore, Stingl has grown the cells described in the paper from EpCAM+ cells. EpCAM, an epithelial cell adhesion molecule, is present only in terminally differentiated tissue, and at best tissue-specific progenitors. In other words, Stingl has overstated the case based upon the evidence. Please see the website below (hard copy of paper enclosed):

http://www.nature.com/nm/journal/v14/n12/full/nm.1791.html

In this 2008 paper, in which Stingl is also a senior author, it is clearly stated that EpCAM+ cells ARE NOT in any way stem cells (see quote below).

"Most primary luminal-restricted CFCs (72 ±10%) were confined to the CD49f$^+$EpCAM$^+$ fraction, whereas most primary bipotent (77% ±11%) and myoepithelial-restricted (97 ±2%) CFCs were concentrated in the CD49f$^+$EpCAM$^{neg-low}$ fraction (Fig. 3c)."

In other words, Stingl has made an error in his earlier paper cited by the examiner, and was growing at best a bipotent tissue-specific progenitor, and therefore NOT a stem cell.

In addition, besides not fulfilling the claimed requirement of being pluripotent progenitor cells, the precursor cells in Stingl were not isolated from human mammary secretion (of lactating mothers), but from breast tissue. There is no suggestion in Stingl to isolate cells from human mammary secretion instead of breast tissue, let alone any suggestion that pluripotent progenitor cells could be found there.

Pluripotent progenitor cells isolated from human mammary secretion are not disclosed in Stingl et al., nor in any other prior art document, and are therefore a new product.

2. Arguments for non-obviousness of claim 1:

Young et al.:

With respect to the paper of Young et al. itself, I respectfully refer to my previous declaration dated August 20, 2008 and kindly ask the examiner to reconsider my arguments.

The publication by Young et al. discloses cellular components identified in the milk of the tammar wallaby. Said components include macrophages, neutrophils, lymphocytes and other vacuolated mononuclear cells (see abstract). The cells isolated in Young et al. are terminally differentiated blood cells, as compared to pluripotent stem cells, which have the ability to differentiate into various different cell types of an organism. By saying that the cells found were eosinophils, besides the macrophages, neutrophils and lymphocytes found, the reader skilled in the art derives from the publication only the information that various different immune cells were found in the milk of a tammar wallaby.

Differences of claim 1 to Young et al.:

Besides failing to disclose the isolation of pluripotent progenitor cells, Young also fails to disclose the isolation of cells from human mammary secretion.

Non-obviousness over Young et al.:

Besides the isolation of pluripotent progenitor cells and the isolation of cells from human mammary secretion not being disclosed in Young et al., these features are also not suggested anywhere in Young et al.

No motivation to combine Young et al. with Stingl et al.:

A person skilled in the art, starting from Young, who discusses the isolation of immune cells (which are blood cells) from the milk of a tammar wallaby (a small member of the kangaroo family) and their role in immunological protection of the young animal, would have no motivation to turn to Stingl, who describes the isolation of primitive epithelial precursor cells from human breast tissue.

Neither the focus of the paper, nor the source of the cells, nor the species, nor the type of cells isolated is congruent between these two documents. None of the two documents concerns the isolation of cells from human mature milk and none of them concerns the isolation of pluripotent progenitor cells. For example, a person seeking to isolate pluripotent progenitor cells would not turn to Stingl, as this document concerns epithelial precursor cells. Likewise, a person seeking to isolate cells from human milk instead of milk of the tammar wallaby, would not turn to Stingl either, as this document concerns the isolation of cells from human breast tissue.

Summary:

I therefore hereby submit that I respectfully disagree with the examiner's statement that the publication by Stingl et al. is novelty-destroying for claim 18, and also respectfully submit that the present invention according to claim 1 is non-obvious based on Young et al. in view of Stingl et al.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true.

Baar, 22.6.09
Place, Date

Mark Cregan